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Original article

Is tumor bed boost necessary in patients who achieved ypCR following neoadjuvant chemotherapy and breast conserving therapy? (KROG 12-05 and 16-16)

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ABSTRACT

Purpose: This multi-institutional study intended to investigate the effect of tumor bed boost in patients who achieved pathologic complete response (ypCR) following neoadjuvant chemotherapy (NAC) and breast-conserving therapy (BCT).
Materials and methods: We identified 180 patients who initially had lymph node (LN) metastasis and achieved ypCR (ypT0/isN0) following NAC and BCT from the 13 institutions of the Korean Radiation Oncology Group (KROG) 16-16 and KROG 12-05. The effect of tumor bed boost on loco-regional control (LRC), disease-free survival (DFS), and overall survival (OS) rates was analyzed.
Results: In all patients, five-year LRC, DFS and OS rates were 97.5%, 95.4%, and 99.4%, respectively. Tumor bed boost was performed in 158 (87.8%) patients. Advanced N-stage (cN2-3, $p = 0.036$), close resection margin ($p < 0.001$), and sentinel lymph node biopsy ($p = 0.040$) were unfavorable factors for DFS. Tumor bed boost was not a significant factor for LRC, DFS, and OS.

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Conclusions: This study suggests the benefit of tumor bed boost might be minimal in ypCR patients following NAC and BCT. Larger prospective studies are needed to address this issue.

1. Introduction

Neoadjuvant chemotherapy (NAC) for breast cancer is advantageous in terms of increasing the likelihood of successful breast-conservation treatment (BCT) [1,2]. Furthermore, NAC gives opportunity to assess response to chemotherapy and this response can be used to predict survival [3]. The patients who achieved pathologic complete remission (ypCR) following NAC have lower rate of loco-regional recurrence (LRR), and greater disease-free survival (DFS) and overall survival (OS) [4]. A pooled analysis reported that ypCR (ypT0/isN0) was a powerful prognostic factor for survival in patients who received NAC and surgery for breast cancer [5]. In order to investigate the optimal radiation therapy (RT) strategies for ypCR patients, several retrospective studies have been performed, however, there is not yet any established guideline for these patients [6,7].

Local recurrence following BCT is located near primary tumor in 44–90% patients [8–10]. A pathological study of mastectomy specimen also revealed that approximately 90% of microscopic residual disease was present within 4 cm from the primary tumor [11]. The European Organization for Research and Treatment of Cancer (EORTC) 22881-10882 trial and Lyon boost trial showed that the 10–16 Gy additional RT to primary tumor bed reduced incidence of ipsilateral breast tumor recurrence (IBTR) without any survival benefit in patients who received breast-conserving surgery (BCS) and whole breast RT [12–14]. Based on these trials, the contemporary guidelines recommend tumor bed boost in most patients following BCT [15]. However, dramatic advances have been made in systemic therapy since these studies were performed, and the absolute benefit of tumor bed boost is probably less than it was in the EORTC or Lyon trial [16,17].

In NAC setting, the patients who achieved ypCR following NAC have a very low risk of local recurrence, and the significance of tumor bed boost in these patients needs to be validated. We previously performed two multi-institutional studies to identify the role of elective nodal irradiation (ENI) in ypN0 patients following NAC and surgery for breast cancer (Korean Radiation Oncology Group (KROG) 12-05 and KROG 16-16) [7]. Using these data, this study intended to evaluate the influence of tumor bed boost in patients who achieved ypCR following NAC and BCT.

2. Materials and methods

2.1. Patients

We identified 180 patients who initially had lymph node (LN) metastasis and achieved ypT0/isN0 following NAC and BCT in 13 institutions of KROG from 1993 to 2011. Fig. 1 describes the process of selecting the study cohort. This study was approved by Institutional Review Board of each participating institution. Axillary LN confirmation with fine-needle aspiration (FNA) before NAC was performed in 72 (40.0%) patients, and node-positivity in the remaining patients was based upon either positron emission tomography-computed tomography, magnetic resonance imaging, or ultrasonography.

2.2. Treatment

All of the patients were treated with NAC followed by BCS and whole breast RT. The most frequently used regimen for NAC was anthracycline plus taxane (AT, N = 57, 31.7%), followed by anthracycline and cyclophosphamide (AC) combined with taxane (N = 39, 21.7%), and AC (31, 17.2%, Table 1). Axillary LN dissection (ALND) was performed in 155 (86.1%) patients, while 25 (13.9%) patients only received sentinel LN biopsy (SLNB) after NAC. Adjuvant chemotherapy was delivered to 91 (50.0%) patients. The most common regimen was AT (N = 34, 37.4%) followed by AC (N = 22, 24.2%). Adjuvant hormone treatment was administrated to 49 (27.2%) patients. Among the HER2-positive tumors (N = 93), HER2-targeted therapy was delivered to 57 (61.3%) patients. Adjuvant RT dose to whole breast was 45–54 Gy by 1.8–2.0 Gy per fraction. The boost RT to primary tumor bed was delivered in 158 (87.8%) patients and the dose schedule for boost was 9–14 Gy by 1.8–3.5 Gy per fraction. When the biologically equivalent dose (BED) to tumor bed was calculated using alpha/beta ratio of 4 for breast cancer cells, median BED to tumor bed in patients who did and did not receive tumor bed boost was 88.1 (77.5–93.3) Gy_4 and 74.1 (67.9–75) Gy_4, respectively. ENI including the supraclavicular region was performed in 86 (47.8%) patients. The RT dose to ENI was 45–54 Gy by 1.8–2.0 Gy per fraction. Close resection margin was defined as tumor cells seen within less than 1 mm of the resection margin.

2.3. Statistical analysis

The distributions of categorical variables between the patients who did or did not receive tumor bed boost were compared using Chi-square tests or Fisher's exact tests. LRR was defined as any first recurrence in ipsilateral breast or ipsilateral axillary, supraclavicular, or internal mammary LNs. Loco-regional control rate (LRC) was defined as the time from the initiation of NAC to the first

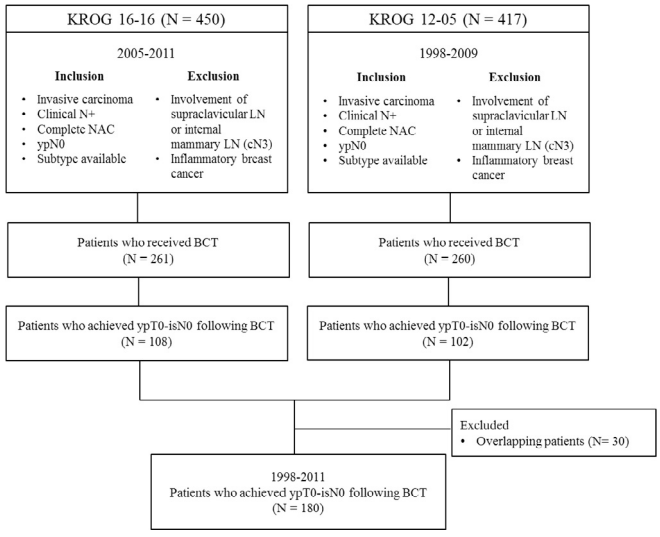

Fig. 1. Flowchart of the patient selection process. NAC, neoadjuvant chemotherapy; LN, lymph node; BCT, breast-conserving treatment.

Table 1
Patient characteristics according to primary tumor bed boost.

	All patients	No boost (n = 22)	Boost (n = 158)	*p*-value
Age				0.516
<50 years	103 (57.2%)	14 (63.6%)	89 (56.3%)	
≥50 years	77 (42.8%)	8 (36.4%)	69 (43.7%)	
Pathology				0.314
IDC	173 (96.1%)	22 (100%)	151 (95.6%)	
Others	7 (3.9%)	0	7 (4.4%)	
Subtype				0.118
HR + Her2-	17 (9.4%)	3 (13.6%)	14 (8.9%)	
HR + Her2+	33 (18.3%)	2 (9.1%)	31 (19.6%)	
TN	66 (36.7%)	13 (59.1%)	53 (33.5%)	
HR-Her2+	60 (33.3%)	4 (18.2%)	56 (35.4%)	
Unknown	4 (2.2%)	0	4 (2.5%)	
Clinical T-stage				0.839
cT1-2	150 (83.3%)	18 (81.8%)	132 (83.5%)	
cT3-4	30 (16.7%)	4 (19.0%)	26 (16.7%)	
Clinical N-stage				0.079
cN1	127 (70.6%)	12 (54.5%)	115 (72.8%)	
cN2-3	53 (29.4%)	10 (45.5%)	43 (27.2%)	
Axillary dissection				0.201
SLNB	25 (13.9%)	5 (22.7%)	20 (12.7%)	
ALND	155 (86.1%)	17 (77.3%)	138 (87.3%)	
ypT				0.301
ypT0	140 (77.8%)	19 (86.4%)	121 (76.6%)	
ypTis	40 (22.2%)	3 (13.6%)	37 (23.4%)	
Resection margin				0.397
Negative	175 (97.2%)	22 (100%)	153 (96.8%)	
Close	5 (2.8%)	0	5 (3.2%)	
ENI				0.003
No	94 (52.2%)	18 (81.8%)	76 (48.1%)	
Yes	86 (47.8%)	4 (18.2%)	82 (51.9%)	
BED to tumor bed (Gy_4)	88.1 (67.9–93.3)	74.1 (67.9–75)	88.1 (77.5–93.3)	

IDC, invasive ductal carcinoma; HR, hormone receptor; TN, triple negative; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ENI, elective nodal irradiation; BED, biologically equivalent dose.

LRR. DFS was defined as the time from the initiation of NAC to relapse or death. OS was defined as the time from the initiation of chemotherapy to death from any cause. The survival curves were estimated using the Kaplan–Meier method and were compared using log-rank tests. Factors that showed a p-value < 0.1 in univariate analysis and BED to tumor bed as a continuous variable were included to multivariate analysis. Cox proportional hazards model was used to perform multivariate analysis and calculate the hazard ratios (HR) and 95% confidence intervals (CI) for LRC, DFS, and OS. A p-value < 0.05 was considered to be statistically significant. We conducted all analyses using SPSS Statistics version 22 (SPSS Inc., an IBM Company, USA).

3. Results

3.1. Patient characteristics according to tumor bed boost

Among all patients, 22 patients (12.2%) did not receive tumor bed boost. The characteristics according to the tumor bed boost are described in Table 2. Advanced clinical N-stage (cN2-3) was more frequent in patients who did not receive boost RT than in those who did (45.5% vs. 27.2%, p = 0.079). ENI was more frequently applied in patients who received boost RT (51.9% vs. 18.2%, p = 0.003). The distribution of other factors including age, pathology, molecular subtypes, clinical T-stage, axillary dissection, resection margin, and ENI did not differ between the groups.

3.2. Prognostic factors for LRC, DFS, and OS

The median follow-up duration was 75 months (range 16–129). The 5-year LRC, DFS and OS rates were 97.5%, 95.4% and 99.4%, respectively (Fig. 2). Among eight recurrent cases, four were isolated LRR while four were distant metastasis (Table 3). The prognostic factors for LRC, DFS, and OS were analyzed by univariate analyses including age, molecular subtypes, cT stage, cN stage, ypT stage, resection margin, axillary dissection, ENI, and boost RT

Table 2
Characteristics and treatment of patients who developed recurrence.

Age	Path	ER	PR	HER2	c-stage	Axillary dissection	ypT-stage	RM	ENI	Boost	Site of Recurrence	Status	Salvage treatment	Disease-free interval	Boost dose scheme
30	IDC	(−)	(−)	(−)	cT2N1	ALND	ypT0	(−)	N	Y	Local recurrence	alive	Surgery	12.5 months	10Gy/4Fx's
35	IDC	(−)	(−)	(+)	cT2N1	ALND	ypT0	(−)	Y	Y	Local recurrence	alive	Surgery	25.5 months	10Gy/5Fx's
42	IDC	(−)	(−)	(−)	cT2N2	SLNB	ypT0	(−)	Y	Y	Local/Axilla	death	CTx	18.0 months	9Gy/3Fx's
55	IDC	(+)	(+)	(+)	cT2N2	ALND	ypTis	(−)	Y	Y	SCN	alive	CTx	42.0 months	9Gy/3Fx's
25	IDC	(−)	(−)	(+)	cT3N2	ALND	ypTis	close	N	Y	DM (lung, brain)	death	CTx	30.0 months	9Gy/3Fx's
45	IDC	(+)	(+)	(+)	cT3N2	SLNB	ypTis	close	N	Y	DM (brain)	alive	RT	11.0 months	10.5Gy/3Fx's
48	IDC	(−)	(−)	(−)	cT2N1	SLNB	ypT0	(−)	N	Y	DM (bone)	alive	RT	53.0 months	10Gy/5Fx's
57	IDC	(−)	(−)	(−)	cT4N3	ALND	ypT0	(−)	N	Y	DM (distal LN)	alive	unknown	16.0 months	10Gy/5Fx's

IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RM, resection margin; ENI, elective nodal irradiation; SCN, supraclavicular lymph node; DM, distant metastasis; CTx, chemotherapy; RT, radiation therapy.

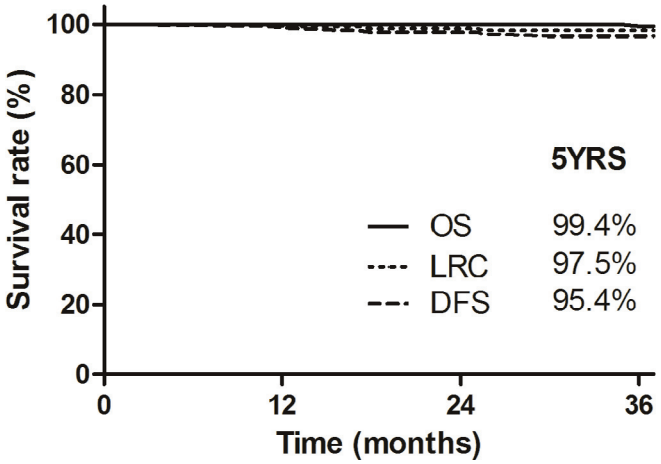

Fig. 2. Survival curves of overall survival (OS), loco-regional control (LRC), and disease-free survival (DFS) and OS, LRC, DFS at 5 years in all patients.

Table 3
Prognostic factors for loco-regional control, disease-free survival, and overall survival by univariate analysis.

	5-LRC	p	5-yr DFS	p	5-yr OS	p
Age		0.496		0.305		0.230
<50 (n = 103)	96.8%		93.9%		99.0%	
≥50 (n = 77)	98.4%		97.2%		100%	
Subtype		0.927		0.780		0.941
HR + Her2- (n = 17)	100%		100%		100%	
HR + Her2+ (n = 33)	96.6%		93.6%		100%	
TN (n = 66)	96.9%		93.7%		98.4%	
HR-Her2+ (n = 60)	98.3%		96.6%		100%	
Unknown (n = 4)	100%		100%		100%	
cT		0.379		0.502		0.190
T1-2 (n = 150)	97.2%		95.8%		99.3%	
T3-4 (n = 30)	100%		93.1%		100%	
cN		0.348		0.036		0.022
N1 (n = 127)	98.4%		97.5%		100%	
N2-3 (n = 53)	95.9%		90.4%		98.0%	
ypT		0.887		0.286		0.270
T0 (n = 140)	97.8%		96.3%		99.2%	
Tis (n = 40)	97.2%		92.2%		100%	
Resection margin		0.765		<0.001		<0.001
Negative (n = 175)	97.6%		96.4%		99.4%	
Close (n = 5)	100%		60.0%		50.0%	
Axillary dissection		0.475		0.040		0.058
SLNB (n = 25)	95.7%		87.0%		95.5%	
ALND (n = 155)	98.0%		96.7%		100%	
ENI		0.302		0.512		0.965
No (n = 94)	98.9%		94.4%		100%	
Yes (n = 86)	96.5%		96.5%		98.8%	
Tumor bed boost		0.467		0.300		0.628
No (n = 22)	100%		100%		100%	
Yes (n = 158)	97.4%		95.5%		99.3%	

LRC, loco-regional control; DFS, disease-free survival; OS, overall survival; HR, hormone receptor; TN, triple negative; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ENI, elective nodal irradiation.

(Table 3). Tumor bed boost was not a significant factor for LRC (p = 0.467), DFS (p = 0.300), and OS (p = 0.628). In multivariate analysis, significant factors for DFS were cN2-3 (HR 5.086, 95% CI 1.193–21.674, p = 0.028), close resection margin (HR 18.979, 95% CI 3.295–109.325, p = 0.001), and SLNB only (HR 6.241, 95% CI 1.373–28.369, p = 0.018, Table 4). Neither tumor bed boost nor tumor bed BED as a continuous variable, was not a significant factor for LRC, DFS, or OS in multivariate analysis.

4. Discussion

This retrospective study suggests that the tumor bed boost might not be beneficial in patients who achieved ypCR following NAC and BCT. By virtue of advance in systemic chemotherapy, LRC has improved and whether the benefit of tumor bed boost remains even in modern chemotherapy era is questionable. Indeed, a recent trial, 'Young boost trial' reported a much lower LRR (1.2% at 5 years) compared to that of earlier EORTC trials (10.2% at 10 years) in adjuvant chemotherapy setting [18]. Furthermore, the use of NAC enabled in vivo assessment of tumor response to chemotherapy. If primary gross tumor has disappeared after NAC, the surrounding microscopic disease, the main target of the tumor bed boost, might also have been eliminated. Accordingly, we hypothesized that the benefit of additional boost RT could be minimal in ypCR patients. Bartelink et al. also suggested that in NAC era, the benefit of boost RT might not be necessary for chemotherapy-responsive tumors which have much lower LRR rate [14]. The LRC rate of the current study was excellent (97.5% at five years), and it did not differ between those who did and did not receive tumor bed boost in both uni-and multi-variate analyses.

In adjuvant radiotherapy after surgery followed by chemotherapy, much effort has been made to identify the patients who would benefit from tumor bed boost and who might not benefit from boost RT among those receiving BCS [19,20]. As a result, tumor bed boost is highly recommended for younger women (<40 years old) with high-grade tumors, close resection margins, larger tumors, hormone receptor negative, and extensive intraductal component [20,21], while tumor bed boost remains optional for patients over 60 years old with small, low-grade, hormone-receptor-positive tumors [22]. In NAC setting, in addition to the established prognostic factors, chemotherapy responsiveness should be incorporated to predict the risk of local recurrence and the benefit of tumor bed boost. In the current study, RT associated factors - ENI and tumor bed boost – did not affect either the LRC or DFS. Interestingly, although the patients who did not receive the tumor bed boost had more unfavorable factors than those who did receive the boost RT, no one developed recurrence among those who had tumor bed boost omitted.

This study has a few limitations owing to its retrospective nature. Due to the long period of the study, NAC regimens were heterogeneous, and HER2-targeted therapy was not applied for all HER2+ patients. Secondly, the number of patients who had tumor bed boost omitted in the current study was too small to draw any

Table 4
Prognostic factors for disease free survival and overall survival by multivariate analysis.

	LRC		DFS		OS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
cN-stage (N2-3 vs. N1)	–	0.483	4.194 (0.977–18.002)	0.054	–	0.547
Resection margin (Close vs. Negative)	–	0.992	22.676 (3.894–132.059)	0.001	–	0.935
Axillary dissection (SLNB vs. ALND)	–	0.473	5.354 (1.175–24.403)	0.030	–	0.951
Tumor bed BED[a]	–	0.237	–	0.321	–	0.640

LRC, loco-regional control; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; BED, biologically equivalent dose.

[a] Tumor bed BED was included in Cox proportional model as a continuous variable.

conclusions regarding the necessity of tumor bed boost. Furthermore, we could not acquire detailed information regarding the precise locations of recurrences – primary tumor site or not – or actually irradiated dose distributions. Nevertheless, to the best of our knowledge, this study is the first study to address the prognostic significance of tumor bed boost in ypCR patients following NAC and BCT. Avoiding unnecessary boost RT can minimize toxicities and promote the efficient use of medical resources [23,24]. In an EORTC trial [8], severe fibrosis was more frequently observed in the boost group (4.4% at 10 years vs. 1.6%, $p < 0.0001$), and the Lyon trial [12] also showed that the rate of $\geq$ grade 1 telangiectasia was higher in those who received boost (12.4% vs 5.9%, $p = 0.003$). Also, radio-sensitivity might be considered in applying additional RT. A recent study reported that the effect of RT depends on tumor biology and suggests that inappropriate RT to radio-resistant tumors might be a waste of medical resources. Further investigations to develop gene profiles that can predict radio-sensitivity might enable more individualized applications of boost RT in the future [25,26].

In summary, the benefit of tumor bed boost in ypCR patients was not demonstrated in this study. However, the effect of tumor bed boost need to be further investigated in larger studies.

Ethical approval

The study was approved by institutional review boards from all the participating institutions and informed consent was not required.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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